Efficacy of brain natriuretic peptide vs nicorandil in preventing contrast-induced nephropathy: a network meta-analysis (#66761)

First submission

Guidance from your Editor

Please submit by **17 Jan 2022** for the benefit of the authors (and your $200 publishing discount) .

Structure and Criteria
Please read the 'Structure and Criteria' page for general guidance.

Custom checks
Make sure you include the custom checks shown below, in your review.

Author notes
Have you read the author notes on the guidance page?

Raw data check
Review the raw data.

Image check
Check that figures and images have not been inappropriately manipulated.

Privacy reminder: If uploading an annotated PDF, remove identifiable information to remain anonymous.

Files

Download and review all files from the materials page.

8 Figure file(s)
5 Table file(s)
2 Raw data file(s)
1 Other file(s)

Custom checks

Systematic review or meta analysis

- Have you checked our policies?
- Is the topic of the study relevant and meaningful?
- Are the results robust and believable?

Human participant/human tissue checks

- Have you checked the authors ethical approval statement?
- Does the study meet our article requirements?
- Has identifiable info been removed from all files?
- Were the experiments necessary and ethical?

Structure and Criteria

Structure your review

The review form is divided into 5 sections. Please consider these when composing your review:

1. **BASIC REPORTING**
2. **EXPERIMENTAL DESIGN**
3. **VALIDITY OF THE FINDINGS**
4. General comments
5. Confidential notes to the editor

You can also annotate this PDF and upload it as part of your review

When ready submit online.

Editorial Criteria

Use these criteria points to structure your review. The full detailed editorial criteria is on your guidance page.

BASIC REPORTING

- Clear, unambiguous, professional English language used throughout.
- Intro & background to show context. Literature well referenced & relevant.
- Structure conforms to PeerJ standards, discipline norm, or improved for clarity.
- Figures are relevant, high quality, well labelled & described.
- Raw data supplied (see PeerJ policy).

EXPERIMENTAL DESIGN

- Original primary research within Scope of the journal.
- Research question well defined, relevant & meaningful. It is stated how the research fills an identified knowledge gap.
- Rigorous investigation performed to a high technical & ethical standard.
- Methods described with sufficient detail & information to replicate.

VALIDITY OF THE FINDINGS

- Impact and novelty not assessed. *Meaningful* replication encouraged where rationale & benefit to literature is clearly stated.
- All underlying data have been provided; they are robust, statistically sound, & controlled.
- Conclusions are well stated, linked to original research question & limited to supporting results.

Standout reviewing tips

The best reviewers use these techniques

Tip	*Example*
Support criticisms with evidence from the text or from other sources	*Smith et al (J of Methodology, 2005, V3, pp 123) have shown that the analysis you use in Lines 241-250 is not the most appropriate for this situation. Please explain why you used this method.*
Give specific suggestions on how to improve the manuscript	*Your introduction needs more detail. I suggest that you improve the description at lines 57- 86 to provide more justification for your study (specifically, you should expand upon the knowledge gap being filled).*
Comment on language and grammar issues	*The English language should be improved to ensure that an international audience can clearly understand your text. Some examples where the language could be improved include lines 23, 77, 121, 128 – the current phrasing makes comprehension difficult. I suggest you have a colleague who is proficient in English and familiar with the subject matter review your manuscript, or contact a professional editing service.*
Organize by importance of the issues, and number your points	*1. Your most important issue* *2. The next most important item* *3. …* *4. The least important points*
Please provide constructive criticism, and avoid personal opinions	*I thank you for providing the raw data, however your supplemental files need more descriptive metadata identifiers to be useful to future readers. Although your results are compelling, the data analysis should be improved in the following ways: AA, BB, CC*
Comment on strengths (as well as weaknesses) of the manuscript	*I commend the authors for their extensive data set, compiled over many years of detailed fieldwork. In addition, the manuscript is clearly written in professional, unambiguous language. If there is a weakness, it is in the statistical analysis (as I have noted above) which should be improved upon before Acceptance.*

Efficacy of brain natriuretic peptide vs nicorandil in preventing contrast-induced nephropathy: a network meta-analysis

Ziwei Mei [1], **Songmei Luo** [1], **Peipei Chen** [1], **Qiankun Zhang** [1], **Limei Zhou** [1], **Chaoyong Zhu** [1], **Hong Zhu** [Corresp., 1], **Lie Jin** [Corresp. 1]

[1] lishui central hospital, Zhejiang, China

Corresponding Authors: Hong Zhu, Lie Jin
Email address: lszxyyzhuhong@163.com, lijie1022@163.com

This study aimed to conduct a network meta-analysis to compare the efficacy of brain natriuretic peptide vs nicorandil for preventing contrast-induced nephropathy(CIN). Databases of Pubmed, Cochrane, Embase, Web of Science were searched by keywords for eligible studies of randomized controlled trials investigating different agents(BNP, nicorandil, nitroglycerin, intravenous saline) for preventing CIN. The outcomes included a chang in serum creatinine at 48 hours and the incidence of CIN after percutaneous coronary intervention(PCI) or coronary angiography(CAG). A total of 13 studies with 3462 patients were included. Compare with intravenous saline alone, intravenous saline plus pharmacological drugs significantly reduced serum creatinine at 48 hours, with mean differences of -5.13 (95%Cl:-14.33,4.07) for nitroglycerin, -7.14 (95%Cl:-11.34,-2.94) for BNP, -5.57 (95%Cl:-8.93,-2.20) for usual-dose nicorandil, -10.08(95%Cl:-17.42,-2.74) for double-dose nicorandil, and decreased the incidence of CIN (nitroglycerin of OR,1.02[95%Cl:0.36, 2.88]; BNP of OR,0.35[95%Cl:0.24,0.51]; usual-dose nicorandil of OR, 0.35[95%Cl:0.24, 0.51]; double-dose nicorandil of OR, 0.27[95%Cl: 0.11, 0.68]). Statistical differences were found in the serum creatinine and the incidence of CIN among these four preventing methods. In conclusion, BNP is more effective for preventing the incidence of CIN than nicorandil.

Efficacy of brain natriuretic peptide vs nicorandil in preventing contrast-induced nephropathy: a network meta-analysis

Ziwei MEI[1], Songmei LUO[1], Peipei CHEN[1], Qiankun ZHANG[2], Limei ZHOU[2], Chaoyong ZHU[2], HONG ZHU[2*], LIE JIN[2*]

Department of [1]Pharmacy and [2] Neurology Lishui Central Hospital, Lishui, China

Ziwei Mei, Department of Pharmacy, Lishui Central Hospital, 323000 Lishui, China. Tel: 17858199601. e-mail: lszxyymzw@163.com

Correspondence: Hong Zhu, Department of Neurology, Lishui Central Hospital, 323000 Lishui, China. Tel: 13506500270. e-mail: lszxyyzhuhong@163.com; Lie Jin, Department of Neurology, Lishui Central Hospital, 323000 Lishui, China. Tel:05782285229, e-mail: lijie1022@163.com

Abstract

This study aimed to conduct a network meta-analysis to compare the efficacy of brain natriuretic peptide vs nicorandil for preventing contrast-induced nephropathy(CIN). Databases of Pubmed, Cochrane, Embase, Web of Science were searched by keywords for eligible studies of randomized controlled trials investigating different agents(BNP, nicorandil, nitroglycerin, intravenous saline) for preventing CIN. The outcomes included a chang in serum creatinine at 48 hours and the incidence of CIN after percutaneous coronary intervention(PCI) or coronary angiography(CAG). A total of 13 studies with 3462 patients were included. Compare with intravenous saline alone, pharmacological drugs combinated intravenous saline significantly reduced serum creatinine at 48 hours, with mean differences of -5.13 (95%Cl:-14.33,4.07) for nitroglycerin, -7.14 (95%Cl:-11.34,-2.94) for BNP, -5.57 (95%Cl:-8.93,-2.20) for usual-dose nicorandil, -10.08(95%Cl:-17.42,-2.74) for double-dose nicorandil, and decreased the incidence of CIN (nitroglycerin of OR,1.02[95%Cl:0.36, 2.88]; BNP of OR,0.35[95%Cl:0.24,0.51]; usual-dose nicorandil of OR, 0.35[95%Cl:0.24, 0.51]; double-dose nicorandil of OR, 0.27[95%Cl: 0.11, 0.68]). Statistical differences were found in the serum creatinine and the incidence of CIN among these four

preventing methods. In conclusion, BNP is more effective for preventing the incidence of CIN than nicorandil.

Keywords: Contrast-induced nephropathy, Brain natriuretic peptide, Nicorandil, Meta-analysis

1. Introduction

Percutaneous coronary intervention(PCI) or coronary angiography(CAG) is common method for treatment and diagnosis of coronary heart disease. However, the application of contrast agents for patients undergoing CAG or PCI usually induce contrast-induced nephropathy(CIN). CIN refers to an abrupt damage in renal function after the administration of contrast agents[1-3]. CIN is a serious complication featured by deterioration of renal function which may lead to water-sodium retention aggravating heart failure and to drug accumulation increasing adverse drug reaction[4]. In the long run, it will induce damage on other organ such as cardiovascular system and digestive system.

With the increased application of contrast agents for radiation diagnosis and interventional therapy, the rate of CIN continues to rise. It has been reported that the incidence of CIN varies from 2% to 50%, it likely more occurred in patients with risk factors, such as pre-existing renal impairment, diabetes mellitus, congestive heart failure, advanced age, and hypertension[5]. CIN is the third most common cause of hospital-acquired acute kidney injury prolonging hospitalization and increasing some poor outcomes, such as dialysis and cardiovascular diseases[6-8]. Therefore, CIN has become one of the important issues affecting the survival and prognosis of patients.

Nowadays, there is no effective method to therapy CIN, therefore more and more studies have been conducted to explore methods for preventing CIN[9,10]. A large number of randomized controlled trials(RCTs) have demonstrated pharmacological drugs counld prevent the incidence of CIN. These years, prostaglandin analogues and BNP analogues are applied to prevent the CIN in the PCI and CAG. Some RCTs showed rhBNP and nicorandil interventions could reduce the incidence of CIN and SCr levels in the PCI and CAG[11,12]. However, there was no study evaluate and compare the efficacy of rhBNP and nicorandil in preventing CIN. This study conducted an NMA of RCTs in order to directly and indirectly compare the efficacy of rhBNP vs nicorandil for

preventing CIN in PCI or CAG.

2. Methods

The protocol of this NMA has been registered on the International Prospective Register of Systematic Review with a registration number of CRD42021278424. We reported this NMA based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for NMA.

2.1 Data sources and searches

Two reviewers (MZW and ZQK) independently searched the literature and disagreements were resolved by consensus-based discussion. We searched an extensive literature from Pubmed, Cochrane, Embase, Web of Science and clinicaltrials.gov databases. The deadline of publication for inclusion in the meta-analysis was August 2021. Our search terms and search strategy were ((nicorandil) OR (brain natriuretic peptide)) AND ((coronary angiography) OR (percutaneous coronary intervention)); (contrast-induced nephropathy) AND ((nicorandil) OR (brain natriuretic peptide)). In addition, references included to related meta-analysis were viewed potential studies.

2.2 Study selection

The final studies were selected by the following inclusion criteria: (1) full-RCTs; (2) evaluating the efficacy of CIN preventing; (3) all patients following PCI or CAG; (4) hydration is the co-intervention in the treatment and control groups; (5) reported sufficient data and at least one of the following outcomes: the incidence of CIN, serum creatinine (SCr) level.

Studies were excluded according the following features: (1) non-RCTs; (2) duplicate publication; (3) animal studies; (4) lacking data about the incidence of CIN and serum creatinine level.

2.3 Endpoint

The primary outcome was CIN defined by an increase in serum creatinine of >0.5mg/dL or >25% from baseline within 48hours after PCI or CAG, but the definition of CIN reported by included study was accepted. The secondary endpoints were changes in the SCr, before and after the procedure. If the SCr value was reported at multiple timepoints, we extracted at the 48h after

procedure.

2.4 Data Extraction and Quality Assessment

There reviewers (ZLM, CPP and ZCY) independently extracted data from original trial reports by a standardized form. By discussion with a third reviewer (JL), discrepancies were settled. The characteristics of the enrolled studies in each group including first author, publication date, country, sample size, baseline characteristics of the patients, incidence of CIN, SCr level were extracted. Each included study was assessed by the risk of bias evaluated tool from the Cochrane Handbook for Randomized Controlled Trials. This assessment was completed independently by two investigators (MZW and ZH) and disagreements were discussed with a third reviewer and resolved through consensus.

2.5 Data analysis

We used network meta-analysis to estimate the treatment effect of pharmacological interventions by the odds ratio(OR) for the incidence of CIN and mean difference(MD) for SCr level at 48h after procedure with a 95% confidence interval(Cl). The treatment hierarchy was summarized and reported according the cumulative ranking curve(SUCRA) and mean ranks. SUCRA was presented as a percentage and used to determine the probability of a treatment being the most effective, without uncertainty on the outcome. The higher probability viewed as the best intervention was the larger surface area under the curve.

Inconsistency was assessed by global inconsistency, loop-specific and node-splitting approach between direct and indirect evidence. In global inconsistency, $P>0.05$ was considered there was no statistical significance about heterogeneity among the evidences. For loop-specific approach, the extent of bias and inconsistency was evaluated by IF. When an IF with a 95% Cl including 0, demonstrated the treatment effect from direct and indirect evidence are in agreement. For node-splitting approach, the result of compared evidence between direct and indirect evidence was reported and P value, $P>0.05$ indicated there is no inconsistency. Statistical analyses were performed using STATA 15.0 (Stata Corporation, College Station, Texas, USA).

3. Results

3.1 Study characteristics

13 RCTs studies were included for analysis after removing the duplicate studies, reviews, non-RCTs, and irrelevant content. The literature search process is shown in Figure 1. Five nodes were included in our NMA shown in Figure 2. The publication year of the included studies ranged from 2014 to 2019. 3462 participants were included totally and female participants accounted for 31.43%. The sample sizes ranged from 128 to 1000. The information and baseline characteristic of the studies are provided in Table1 and Table2. The 13 RCTs contained the following comparisons: BNP vs hydration(n=4), BNP vs nitroglycerin(n=1), nicorandil vs hydration(n=8).

3.2 Quality of the included studies

Most of the studies were judged to be at low risk of bias for 6 domains[13-17], according to the Cochrane Collaboration's tool. 8 studies were judged to be at high risk of bias for they were not blinded[18-25]. One study were judged to be at high risk of bias for participants were randomized according to the participating centers and the severity of the renal dysfunction (eGFR ≤40 or >40 mL/min) [20]. The risk of bias assessment of the trials included in this study is presented in Figure 3.

3.3 Network meta-analysis results

3.3.1 The incidence of CIN

Totally 12 RCTs including 3332 participants were evaluated the effect of pharmacological interventions for the incidence of CIN. Compare with intravenous saline alone, nitroglycerin, BNP, nicorandil plus intravenous saline are shown more effective in reducing the incidence of CIN and there was statistically significant (nitroglycerin of OR,1.02[95%Cl:0.36,2.88]; BNP of OR, 0.35[95%Cl:0.24,0.51]; usual-dose nicorandil of OR, 0.35[95%Cl:0.24, 0.51]; double-dose nicorandil of OR, 0.27[95%Cl: 0.11, 0.68]) (Figure 4). Results of the pairwise comparisons are indicated by the ORs and 95%Cls shown by Figure 5. Double-dose nicorandil was superior to BNP, BNP was associated with lower CIN risk than usual-dose nicorandil.

3.3.2 Efficacy of SCr level after the procedure

Related to the change in the SCr levels, 11 RCTs including 3084 patients were availabled to

the network meta-analysis. We found significant differences in efficacy between all the drugs and the intravenous saline alone. Compared with intravenous saline alone, BNP, nicorandil plus intravenous saline significantly reduced the SCr levels, with mean differences of -5.13(95%Cl:-14.33,4.07) for nitroglycerin, -7.14(95%Cl:-11.34,-2.94) for BNP, -5.57(95%Cl:-8.93,-2.20) for usual-dose nicorandil, -10.08(95%Cl:-17.42,-2.74) for double-dose nicorandil(Figure 6). Double-dose nicorandil was reduce much more than BNP in the SCr levels after procedure. Usual-dose nicorandil was less effect than BNP in reducing the SCr levels after procedure. Results of the pairwise comparison are indicated by the MDs and 95%Cls shown by Figure 5.

3.3.3 Ranking of the CIN occurence and SCr levels of all enrolled agents

The surface under the cumulative ranking(SUCRA) curves are presented in Figure 7. SUCRA was used to rank the efficacy of the drugs interventions in our study. The SUCRA values provide the hierarchy for five interventions that are 12.8, 14.5, 69.5, 68.9, 84.3% of intravenous saline, nitroglycerin, rhBNP, usual-dose nicorandil, double-dose nicorandil for the incidence of CIN(Table 3) and are 3.7%, 45.7%, 66.5%, 48.6%, 85.6% of intravenous saline, nitroglycerin, BNP, usual-dose nicorandil, double-dose nicorandil for reducing the SCr levels(Table 4). According to the SUCRA, double-dose nicorandil plus intravenous saline had the best efficacy in the CIN occurrence and reducing SCr levels, followed by BNP and low-dose nicorandil, whereas intravenous saline ranked worst.

3.3.4 Heterogeneity and inconsistency assessment

All RCTs were tested for the inconsistency assessed by global inconsistency, loop-specific and node-splitting approach between direct and indirect evidence. In global inconsistency, the result of P=0.072(>0.05) was demonstrated there was no statistical significance about heterogeneity among the evidences. For loop-specific approach, the IF is 0.85(95%Cl: 0.00-2.33) indicated the treatment effect from direct and indirect evidence are in agreement. For node-splitting approach, the results are presented in Table 5. P-value>0.05 indicated no inconsistency among the direct and indirect comparisons.

3.3.5 Small-study effect analysis

The results of the comparison-adjusted funnel plots indicated that there may not be small-study effects for efficacy (Figure 8).

4. Discussion

There is a high-risk of the CIN occurrence caused by the administration of contrast agents for patients undergoing CAG and PCI. Periprocedural hydration is the most common method for intervention the incidence of CIN in clinical practical application. For patients with non-dehydration, 500 mL of water was suggested to drink before the contrast examination. In addition, within 24 h contrast exposure administrating 2500 mL of intravenous saline to sustain a urine generation rate over 1 ml/kg/h[26]. This method is effective for prevention the incidence of CIN. However, how much the volume of hydration is sufficient to effectively decrease the incidence of CIN

hasn't been standardized. In addition, the fluids in periprocedural hydration may aggravate disease condition for patients with heart failure or edema and increase arrhythmias and short-term death risk in high risk patient[27,28]. Therefore, researches effort to study the therapy of various pharmacological agents in preventing the incidence of CIN. It indicated that compared with intravenous saline alone, pharmacological agents intervention have better benefits to reduce the occurrence of CIN.

Currently, more recent interventions about prostaglandin analogues and BNP analogues are confirmed that counld prevent the incidence of CIN. It proved BNP have diuretic and natriuretic action by increasing glomerular filtration rate(GFR)[29]. This action makes it improving renal hemodynamics and tubular function[30]. According this pharmacological action, a number of studies have been performed to use BNP to reduce the incidence of CIN in patients undergoing PCI or CAG. Nicorandil is a combination of nicotin amide vitamins and nitrates improving blood flow by opening ATP-sensitive potassium channel and cytoplasmic guanosine cyclase in the kidneys[31,32]. It was shown effective in reducing the incidence of CIN. Whereas there is rare guideline recommend them. One reason probably is inadequate study data could determine the effect of prostaglandin analogues and BNP analogues for preventing the CIN. This study is the

first network meta-analysis to specifically evaluate the efficacy of nicorandil(prostaglandin analogues) and rhBNP(BNP analogues) for preventing the incidence of CIN after PCI and CAG procedure.

In our study, we made some observations from evidence of 13 RCTs with 3462 patients. First, pharmacological agents of rhBNP and nicorandil combinated with intravenous saline were identified to be benefit additionally to reduce the occurrence of CIN and the SCr levels at 48h after PCI and CAG procedure than intravenous saline alone. Nitroglycerine was similar to the intravenous insaline alone in reducing CIN occurrence and SCr levels. It suggested that the current evidence supports the clinical application of rhBNP and nicorandil in PCI and CAG. Second, between nicorandil and rhBNP, double-dose nicorandil had the highest SUCRA ranking in reducing CIN occurrence and SCr levels and rhBNP was second in SUCRA ranking. These findings demonstrated double-dose nicorandil have better efficacy than rhBNP for reducing CIN occurrence and SCr levels. However, rhBNP perform better action than usual-dose nicorandil. Therefore rhBNP is more effect and suitable than nicoradil for usual-dose pharmacological intervention in reducing the incidence of CIN after PCI and CAG. It indicated that more studies can be performed to explore the potential of rhBNP in reducing the incidence of CIN in the future.

The pathophysiology of CIN is may related to the direct nephrotoxic effects and hemodynamic changes induced by contrast agents. Contrast agents have direct cytotoxic effects on renal tubular epithelial cells and vascular endothelial cells. It could increases the level of endothelin and adenosine and decrease release of NO and prostaglandins that trigger medullary ischemia and decline GFR in the kidney[33]. In addition, the administration of contrast agents during PCI or CAG could increases resistance of renal vascular representing sustained vasoconstriction and decrease renal blood flow. The accumulation of contrast agents could creates a osmotic environment that induce cellular apoptosis[34]. In the condition of overpressure and volume expansion, BNP is released from the membrane granules of cardiomyocytes. The contrast medium can be diluted and excreted by the effect of BNP in increasing diuresis and natriuresis. BNP also could increases in GFR by dilating glomerular afferent arteries and constricting the

efferent arteries. Nicorandil as prostaglandin analogues increases the renal blood flow by improving the release of nitric oxide and alleviates the inflammatory reaction by antagonizing the production of intracellular oxygen free radicals. The results of our study proved rhBNP and nicorandil could prevent the incidence of CIN. Although there is difference on the mechanism of reducing the CIN between rhBNP and nicorandil, they all perform important role on improving the renal ischemia. Besides, BNP can aggravates the excretion of contrast agents and nicorandil presents relief of inflammatory reaction. The result of this NMW rhBNP perform better action than usual-dose nicorandil probably because of the excretion produced by rhBNP

Our results presented statistically significant reduction of the occurrence of CIN and SCr levels by pharmacological intervention from RCTs. Previous meta-analysis made by Xuebiao Wei et al[35] summarized the incidence of CIN after intervention with rhBNP from five RCTs with 1441 patients, but limited to study the SCr level change. Past meta-analysis lack comparison study in treat effect and intervention dose between rhBNP and nicorandil for preventing CIN incidence. Compared with these previous reports, there are several advantages to consider in our analysis. First, our study compared the intervention efficacy of rhBNP and nicorandil for CIN prevention and analysed the SCr levels change which previous study hasn't researched. Second, we made dose-effect relationship and comparison between rhBNP and nicorandil. It's important for using pharmacological intervention during the PCI or CAG by appropriate dosage in clinical practice application. In previous study, the efficacy comparison of different dose drugs on reducing the incidence of CIN and SCr levels hasn't been consideration. However, there are some limitations in this study. First, a small number of trials with insufficient participants may affect the accurancy of evaluating the treatment effect. Second, the time of diagnosing the CIN after PCI and CAG varied among studies. Therefore, we analysed one outcome of CIN incidence by odds ratio according the result of included study report. Third, the relationship between CIN and clinical consequences wasn't investigated because of insufficient data.

5. Conclusion

This study is the first network meta-analysis to compare the efficacy of rhBNP, nicorandil,

nitroglycerine and intravenous saline in preventing the occurrence of CIN. Based on direct and indirect comparison, we developed SUCRA ranking of these drugs according to their efficacy on the incidence of CIN and SCr levels. SUCRA ranking indicate rhBNP(1.5ug/kg) perform better efficacy than usual-dose nicorandil in reducing the SCr levels and CIN incidence. Compared with intravenous saline alone, combinated with rhBNP or nicorandil could prevent CIN incidence in PCI and CAG, the efficacy of combinated nitroglycerine was similar to intravenous saline alone. Double-dose nicorandil(10mg) perform better efficacy than rhBNP(1.5ug/kg). Although, the OR of the CIN incidence in rhBNP trials was same as in nicorandil trials,

Funding This work was supported by Zhejiang science and technology program of traditional Chinese medicine (2019ZQ047, 2013ZB148) and Wu Jieping Medical Foundation (320.6750.2020-04-44).

Compliance with ethical standards

Conflict of interest None.

Reference

[1] Rear R, Bell RM, Hausenloy DJ. Contrast-induced nephropathy following angiography and cardiac interventions. Heart. 2016 Apr;102(8):638-48. doi: 10.1136/heartjnl-2014-306962. Epub 2016 Feb 8. PMID: 26857214; PMCID: PMC4819627.

[2] Owen RJ, Hiremath S, Myers A, Fraser-Hill M, Barrett BJ. Canadian Association of Radiologists consensus guidelines for the prevention of contrast-induced nephropathy: update 2012. Can Assoc Radiol J. 2014 May;65(2):96-105. doi: 10.1016/j.carj.2012.11.002. Epub 2014 Feb 20. PMID: 24559602.

[3] Grossman PM, Ali SS, Aronow HD, Boros M, Nypaver TJ, Schreiber TL, Park YJ, Henke PK, Gurm HS. Contrast-induced nephropathy in patients undergoing endovascular peripheral vascular intervention: Incidence, risk factors, and outcomes as observed in the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. J Interv Cardiol. 2017 Jun;30(3):274-280. doi: 10.1111/joic.12379. Epub 2017 Apr 3. PMID: 28370487.

[4] Tepel M, Aspelin P, Lameire N. Contrast-induced nephropathy: a clinical and evidence-based approach. Circulation. 2006 Apr 11;113(14):1799-806. doi: 10.1161/CIRCULATIONAHA.105.595090. PMID: 16606801.

[5] Chyou AC, Thodge A, Feldman DN, Swaminathan RV. Statins in the prevention of contrast-induced nephropathy. Curr Treat Options Cardiovasc Med. 2015 Apr;17(4):375. doi: 10.1007/s11936-015-0375-0. PMID: 25778426.

[6] Ali-Hasan-Al-Saegh S, Mirhosseini SJ, Ghodratipour Z, Sarrafan-Chaharsoughi Z, Rahimizadeh E, Karimi-Bondarabadi AA, Haddad F, Shahidzadeh A, Mahdavi P, Dehghan AM, Tahernejad M, Shahidzadeh A, Dehghan H, Ghanei A, Lotfaliani M, Weymann A, Zeriouh M, Popov AF, Sabashnikov A. Strategies Preventing Contrast-Induced Nephropathy After Coronary Angiography: A Comprehensive Meta-Analysis and Systematic Review of 125 Randomized Controlled Trials. Angiology. 2017 May;68(5):389-413. doi: 10.1177/0003319716661445. Epub 2016 Aug 1. PMID: 27485363.

[7] Uzunhasan I, Yildiz A, Arslan S, Abaci O, Kocas C, Kocas BB, Cetinkal G, Dalgic Y, Karaca OS, Dogan SM. Contrast-Induced Acute Kidney Injury Is Associated With Long-Term Adverse Events in Patients With Acute Coronary syndrome. Angiology. 2017 Aug;68(7):621-626. doi: 10.1177/0003319716676173. Epub 2016 Nov 12. PMID: 28660805.

[8] Grossman PM, Ali SS, Aronow HD, Boros M, Nypaver TJ, Schreiber TL, Park YJ, Henke PK, Gurm HS. Contrast-induced nephropathy in patients undergoing endovascular peripheral vascular intervention: Incidence, risk factors, and outcomes as observed in the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. J Interv Cardiol. 2017 Jun;30(3):274-280. doi: 10.1111/joic.12379. Epub 2017 Apr 3. PMID: 28370487.

[9] Subramaniam RM, Suarez-Cuervo C, Wilson RF, Turban S, Zhang A, Sherrod C, Aboagye J, Eng J, Choi MJ, Hutfless S, Bass EB. Effectiveness of Prevention Strategies for Contrast-Induced Nephropathy: A Systematic Review and Meta-analysis. Ann Intern Med. 2016 Mar 15;164(6):406-16. doi: 10.7326/M15-1456. Epub 2016 Feb 2. PMID: 26830221.

[10] Marenzi G, Cosentino N, Werba JP, Tedesco CC, Veglia F, Bartorelli AL. A meta-analysis of randomized controlled trials on statins for the prevention of contrast-induced acute kidney injury in patients with and without acute coronary syndromes. Int J Cardiol. 2015 Mar 15;183:47-53. doi: 10.1016/j.ijcard.2015.01.046. Epub 2015 Jan 29. PMID: 25662053.

[11] Wei XB, Jiang L, Liu XR, Yu DQ, Tan N, Chen JY, Zhou YL, He PC, Liu YH. Brain natriuretic peptide for prevention of contrast-inducednephropathy: a meta-analysis of randomized controlled trials. Eur J Clin Pharmacol. 2016 Nov;72(11):1311-1318. doi: 10.1007/s00228-016-2135-9. Epub 2016 Oct 1. PMID: 27695914.

[12] Pranata R, Vania R, Alkatiri AA, Firman D, Lukito AA. Nicorandil Reduces the Incidence of Contrast-Induced Nephropathy in Patients Undergoing Coronary Angiography/Intervention - Systematic Review and Meta-Analysis of Randomized Controlled Trials Including GRADE Qualification. Cardiovasc Revasc Med. 2020 Sep;21(9):1121-1127. doi: 10.1016/j.carrev.2020.01.010. Epub 2020 Jan 13. PMID: 31959562.

[13] Fan Y, Wei Q, Cai J, Shi Y, Zhang Y, Yao L, Wang X, Lin S, Li Y, Lv J, Zhou B, Du R. Preventive effect of oral nicorandil on contrast-induced nephropathy in patients with renal insufficiency undergoing elective cardiac catheterization. Heart Vessels. 2016 Nov;31(11):1776-1782. doi: 10.1007/s00380-016-0809-y. Epub 2016 Feb 13. PMID: 26874946.

[14] Xing K, Fu X, Wang Y, Li W, Gu X, Hao G, Miao Q, Li S, Jiang Y, Fan W, Geng W. Effect of rhBNP on renal function in STEMI-HF patients with mild renal insufficiency undergoing primary PCI. Heart Vessels. 2016 Apr;31(4):490-8. doi: 10.1007/s00380-015-0642-8. Epub

2015 Jan 31. PMID: 25637044.
[15] Zeng Z, Fu X, Zhang X, Fu N. Comparison of double-dose vs. usual dose of nicorandil for the prevention of contrast-induced nephropathy after cardiac catheterization. Int Urol Nephrol. 2019 Nov;51(11):1999-2004. doi: 10.1007/s11255-019-02244-9. Epub 2019 Aug 5. PMID: 31385178.
[16] Zhang J, Fu X, Jia X, Fan X, Gu X, Li S, Wu W, Fan W, Su J, Hao G, Jiang Y, Xue L. B-type natriuretic peptide for prevention of contrast-induced nephropathy in patients with heart failure undergoing primary percutaneous coronary intervention. Acta Radiol. 2010 Jul;51(6):641-8. doi: 10.3109/02841851.2010.486804. PMID: 20438292.
[17] Zhang X, Yang S, Zhang P, Fu N. Efficacy of nicorandil on the prevention of contrast-induced nephropathy in patients with coronary heart disease undergoing percutaneous coronary intervention. Coron Artery Dis. 2020 May;31(3):284-288. doi: 10.1097/MCA.0000000000000826. PMID: 31658134.
[18] Fan Z, Li Y, Ji H, Jian X. Efficacy of Oral Nicorandil to Prevent Contrast-Induced Nephropathy in Patients with Chronic Renal Dysfunction Undergoing an Elective Coronary Procedure. Kidney Blood Press Res. 2019;44(6):1372-1382. doi: 10.1159/000503160. Epub 2019 Oct 22. PMID: 31639790.
[19] Iranirad L, Hejazi SF, Sadeghi MS, Jang SA. Efficacy of nicorandil treatment for prevention of contrast-induced nephropathy in high-risk patients undergoing cardiac catheterization: A prospective randomized controlled trial. Cardiol J. 2017;24(5):502-507. doi: 10.5603/CJ.a2017.0028. Epub 2017 Mar 10. PMID: 28281738.
[20] Ko YG, Lee BK, Kang WC, Moon JY, Cho YH, Choi SH, Hong MK, Jang Y, Kim JY, Min PK, Kwon HM; PRINCIPLE Investigators. Preventive effect of pretreatment with intravenous nicorandil on contrast-induced nephropathy in patients with renal dysfunction undergoing coronary angiography (PRINCIPLE Study). Yonsei Med J. 2013 Jul;54(4):957-64. doi: 10.3349/ymj.2013.54.4.957. PMID: 23709432; PMCID: PMC3663233.
[21] Liu JM, Xie YN, Gao ZH, Zu XG, Li YJ, Hao YM, Chang L. Brain natriuretic peptide for prevention of contrast-induced nephropathy after percutaneous coronary intervention or coronary angiography. Can J Cardiol. 2014 Dec;30(12):1607-12. doi: 10.1016/j.cjca.2014.08.012. Epub 2014 Aug 23. PMID: 25418218.
[22] Liu J, Xie Y, He F, Gao Z, Hao Y, Zu X, Chang L, Li Y. Recombinant Brain Natriuretic Peptide for the Prevention of Contrast-Induced Nephropathy in Patients with Chronic Kidney Disease Undergoing Nonemergent Percutaneous Coronary Intervention or Coronary Angiography: A Randomized Controlled Trial. Biomed Res Int. 2016;2016:5985327. doi: 10.1155/2016/5985327. Epub 2016 Feb 2. PMID: 26949703; PMCID: PMC4754465.
[23] Zhang P, Li WY, Yang SC, Fu NK, Liu XG, Zhang X, Cong HL, Lin WH, Tian FS, Lu CZ, Zhang J. Preventive Effects of Nicorandil Against Contrast-Induced Nephropathy in Patients With Moderate Renal Insufficiency Undergoing Percutaneous Coronary Intervention. Angiology. 2020 Feb;71(2):183-188. doi: 10.1177/0003319719841733. Epub 2019 Apr 15. PMID: 30987432.
[24] Nawa T, Nishigaki K, Kinomura Y, Tanaka T, Yamada Y, Kawasaki M, Minatoguchi S.

Continuous intravenous infusion of nicorandil for 4 hours before and 24 hours after percutaneous coronary intervention protects against contrast-induced nephropathy in patients with poor renal function. Int J Cardiol. 2015 Sep 15;195:228-34. doi: 10.1016/j.ijcard.2015.05.078. Epub 2015 May 22. PMID: 26048382.

[25] Sun C, Zhi J, Bai X, Li X, Xia H. Comparison of the efficacy of recombinant human brain natriuretic peptide with saline hydration in preventing contrast-induced nephropathy in patients undergoing coronary angiography with or without concomitant percutaneous coronary intervention. Int J Clin Exp Med. 2015 Aug 15;8(8):14166-72. PMID: 26550389; PMCID: PMC4613074.

[26] Zhang F, Lu Z, Wang F. Advances in the pathogenesis and prevention of contrast-induced nephropathy. Life Sci. 2020 Oct 15;259:118379. doi: 10.1016/j.lfs.2020.118379. Epub 2020 Sep 3. PMID: 32890604.

[27] Nijssen EC, Nelemans PJ, Rennenberg RJ, Theunissen RA, van Ommen V, Wildberger JE. Prophylaxis in High-Risk Patients With eGFR < 30 mL/min/1.73 m2: Get the Balance Right. Invest Radiol. 2019 Sep;54(9):580-588. doi: 10.1097/RLI.0000000000000570. PMID: 31033672.

[28] Nijssen EC, Nelemans PJ, Rennenberg RJ, van der Molen AJ, van Ommen GV, Wildberger JE. Impact on clinical practice of updated guidelines on iodinated contrast material: CINART. Eur Radiol. 2020 Jul;30(7):4005-4013. doi: 10.1007/s00330-020-06719-7. Epub 2020 Feb 27. PMID: 32107605; PMCID: PMC7305084.

[29] Potter LR, Yoder AR, Flora DR, Antos LK, Dickey DM. Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications. Handb Exp Pharmacol. 2009;(191):341-66. doi: 10.1007/978-3-540-68964-5_15. PMID: 19089336; PMCID: PMC4855512.

[30] Holmes SJ, Espiner EA, Richards AM, Yandle TG, Frampton C. Renal, endocrine, and hemodynamic effects of human brain natriuretic peptide in normal man. J Clin Endocrinol Metab. 1993 Jan;76(1):91-6. doi: 10.1210/jcem.76.1.8380606. PMID: 8380606.

[31] Shimizu S, Saito M, Kinoshita Y, Ohmasa F, Dimitriadis F, Shomori K, Hayashi A, Satoh K. Nicorandil ameliorates ischaemia-reperfusion injury in the rat kidney. Br J Pharmacol. 2011 May;163(2):272-82. doi: 10.1111/j.1476-5381.2011.01231.x. PMID: 21250976; PMCID: PMC3087131.

[32] Fan Y, Wei Q, Cai J, Shi Y, Zhang Y, Yao L, Wang X, Lin S, Li Y, Lv J, Zhou B, Du R. Preventive effect of oral nicorandil on contrast-induced nephropathy in patients with renal insufficiency undergoing elective cardiac catheterization. Heart Vessels. 2016 Nov;31(11):1776-1782. doi: 10.1007/s00380-016-0809-y. Epub 2016 Feb 13. PMID: 26874946.

[33] Dugbartey GJ, Redington AN. Prevention of contrast-induced nephropathy by limb isc hemic preconditioning: underlying mechanisms and clinical effects. Am J Physiol Ren al Physiol. 2018 Mar 1;314(3):F319-F328. doi: 10.1152/ajprenal.00130.2017. Epub 201 7 May 31. PMID: 28566501.

[34] McCullough PA, Choi JP, Feghali GA, Schussler JM, Stoler RM, Vallabahn RC, Mehta A.

Contrast-Induced Acute Kidney Injury. J Am Coll Cardiol. 2016 Sep 27;68(13):1465-1473. doi: 10.1016/j.jacc.2016.05.099. PMID: 27659469.

[35] Wei XB, Jiang L, Liu XR, Yu DQ, Tan N, Chen JY, Zhou YL, He PC, Liu YH. Brain natriuretic peptide for prevention of contrast-inducednephropathy: a meta-analysis of randomized controlled trials. Eur J Clin Pharmacol. 2016 Nov;72(11):1311-1318. doi: 10.1007/s00228-016-2135-9. Epub 2016 Oct 1. PMID: 27695914.

Figure 1

Flow chart of literature search and selection

Flow chart of literature search and selection

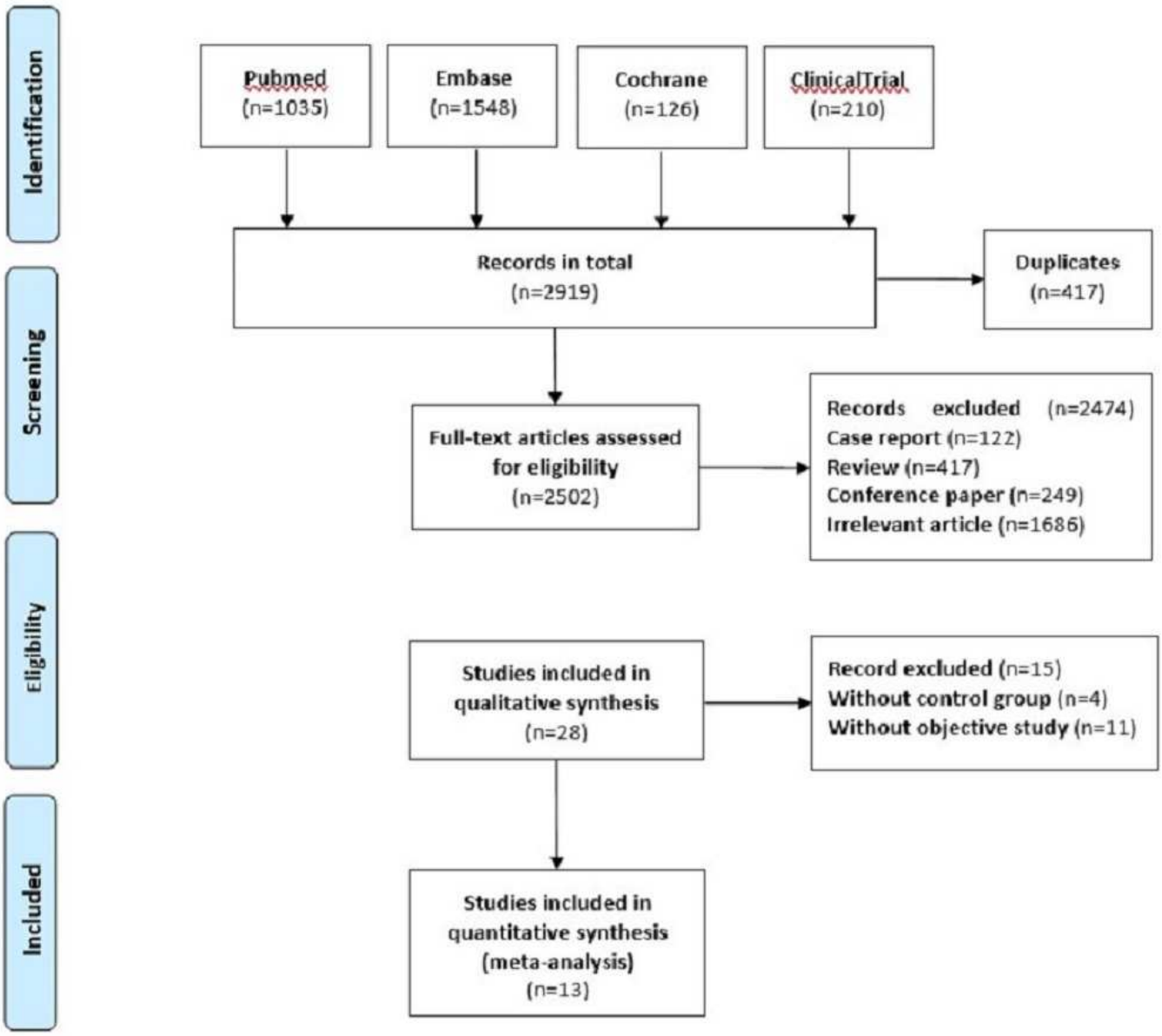

Figure 2

Network of all pharmacological agents included in the analysis. Nodes represent the treatments being compared. The edges indicate direct comparisons and the width is proportional to the number of trials.

Network of all pharmacological agents included in the analysis. Nodes represent the treatments being compared. The edges indicate direct comparisons and the width is proportional to the number of trials.

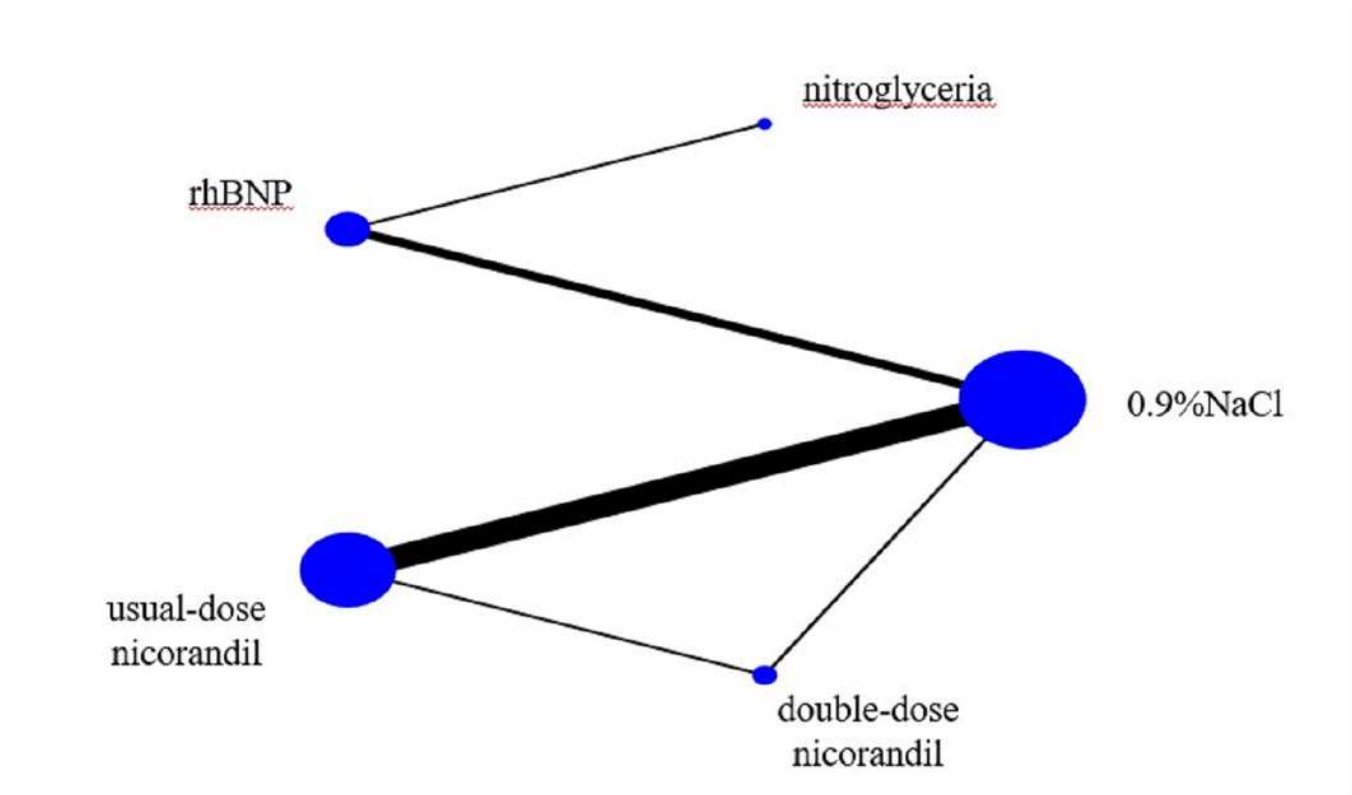

Figure 3

Risk of bias assessment

Risk of bias assessment

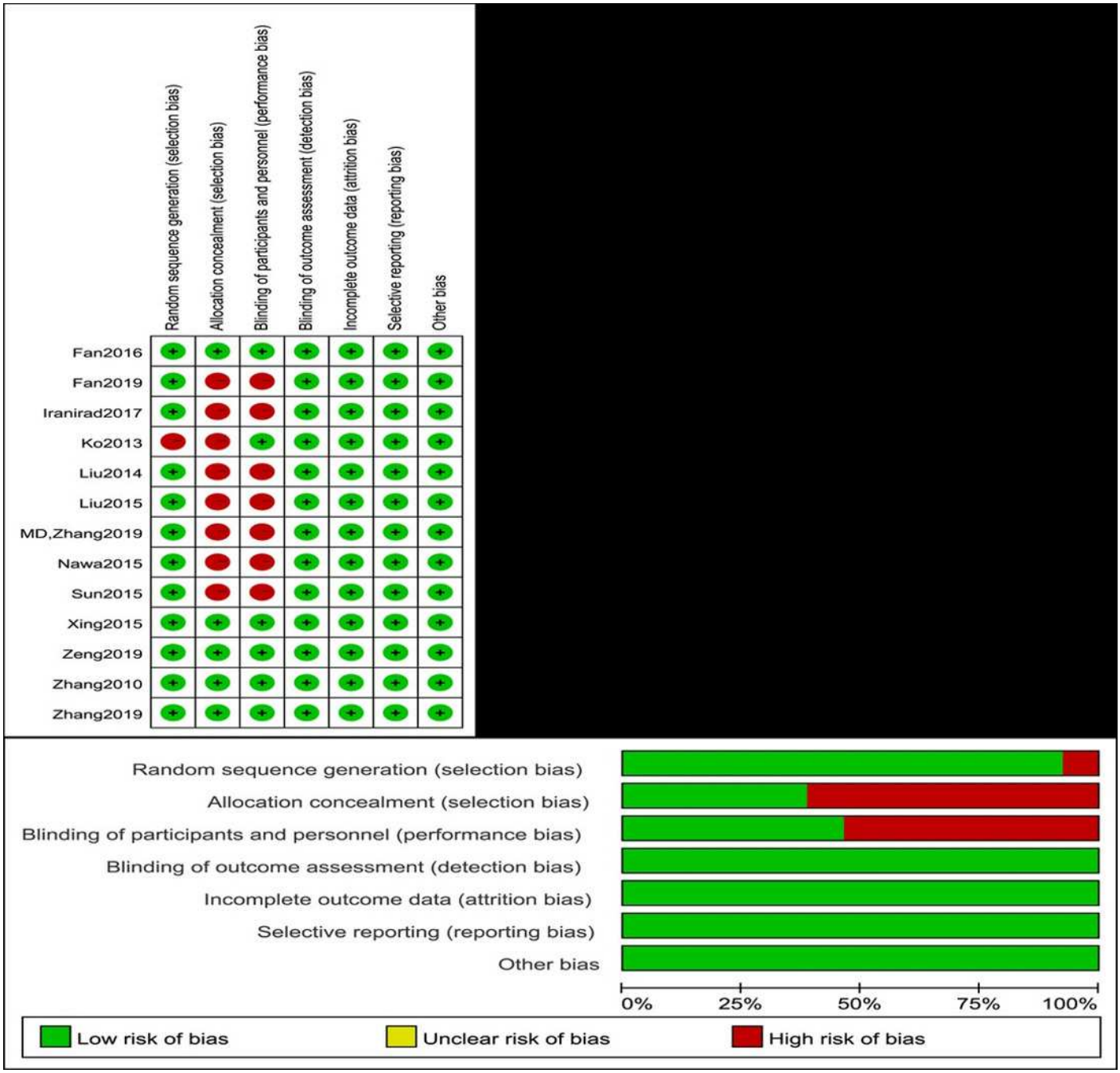

Figure 4

Forest plots of network meta-analysis of all trials for the efficacy of the CIN incidence

Forest plots of network meta-analysis of all trials for the efficacy of the CIN incidence

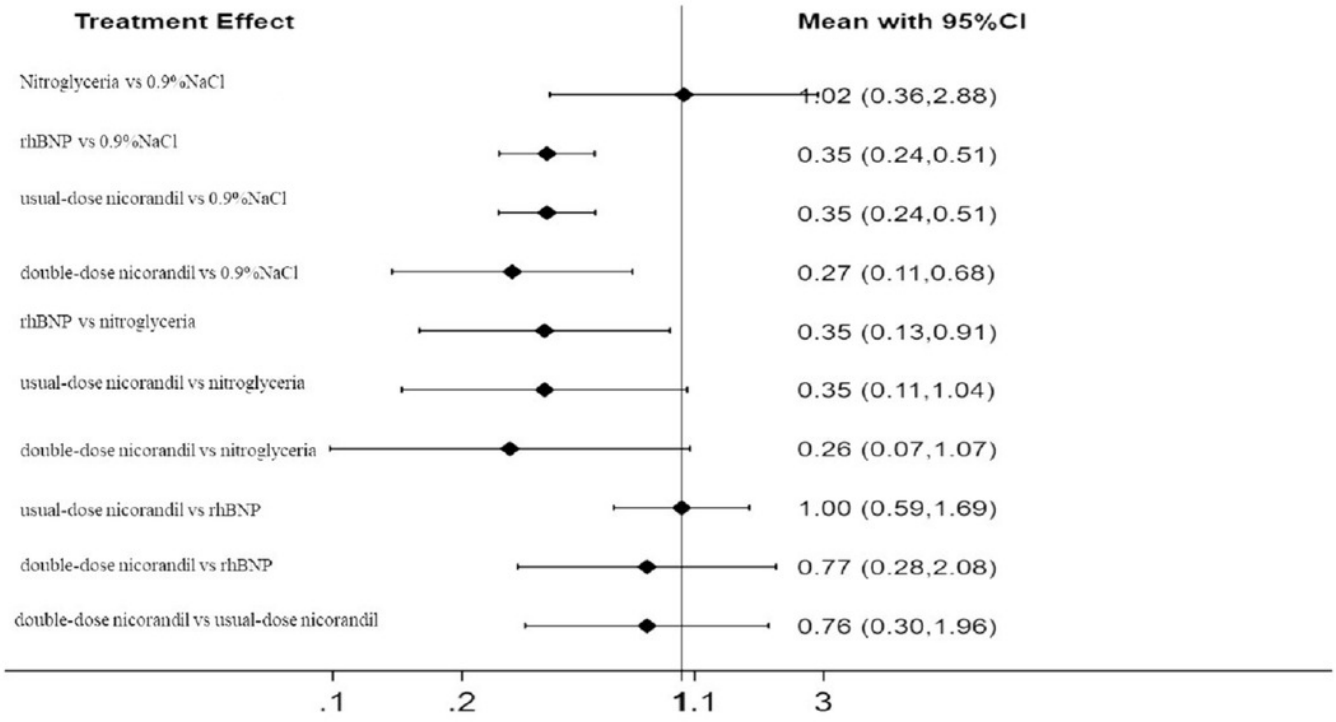

Figure 5

Pairwise comparisons of the efficacy of the thirteen drugs included in the study, reported in alphabetical order. The data represent the ORs, MDs, and 95% CIs in each grid

Pairwise comparisons of the efficacy of the thirteen drugs included in the study, reported in alphabetical order. The data represent the ORs, MDs, and 95% CIs in each grid

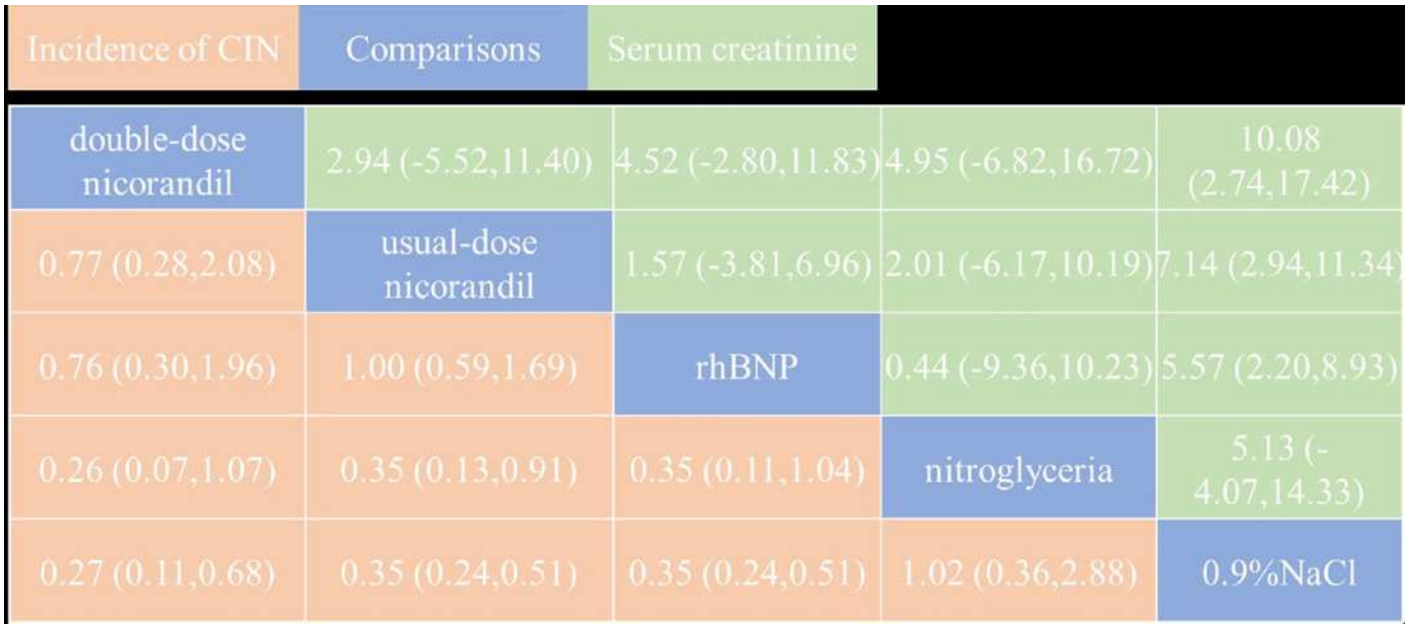

Figure 6

Forest plots of network meta-analysis of all trials for the efficacy of the SCr levels.

Forest plots of network meta-analysis of all trials for the efficacy of the SCr levels.

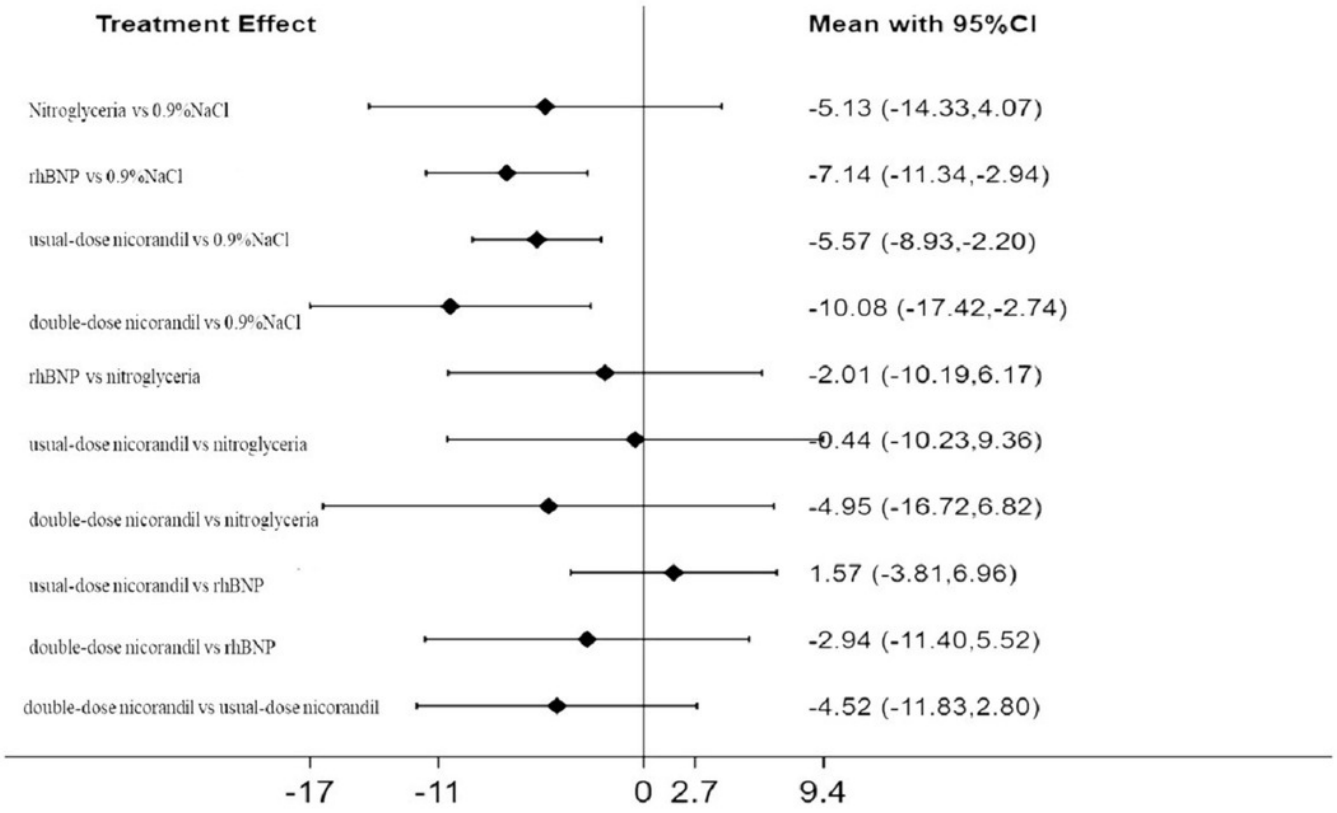

Figure 7

Cumulative ranking probabilities(SUCRA values) for all interventions in the incidence of CIN and SCr levels. Pharmacological intervention is ranked according to SUCRA. The surface area size under the curve indicates the efficient extent of treatment. The

Cumulative ranking probabilities(SUCRA values) for all interventions in the incidence of CIN and SCr levels. Pharmacological intervention is ranked according to SUCRA. The surface area size under the curve indicates the efficient extent of treatment. The larger surface area under the curve represents greater efficacy of the intervention

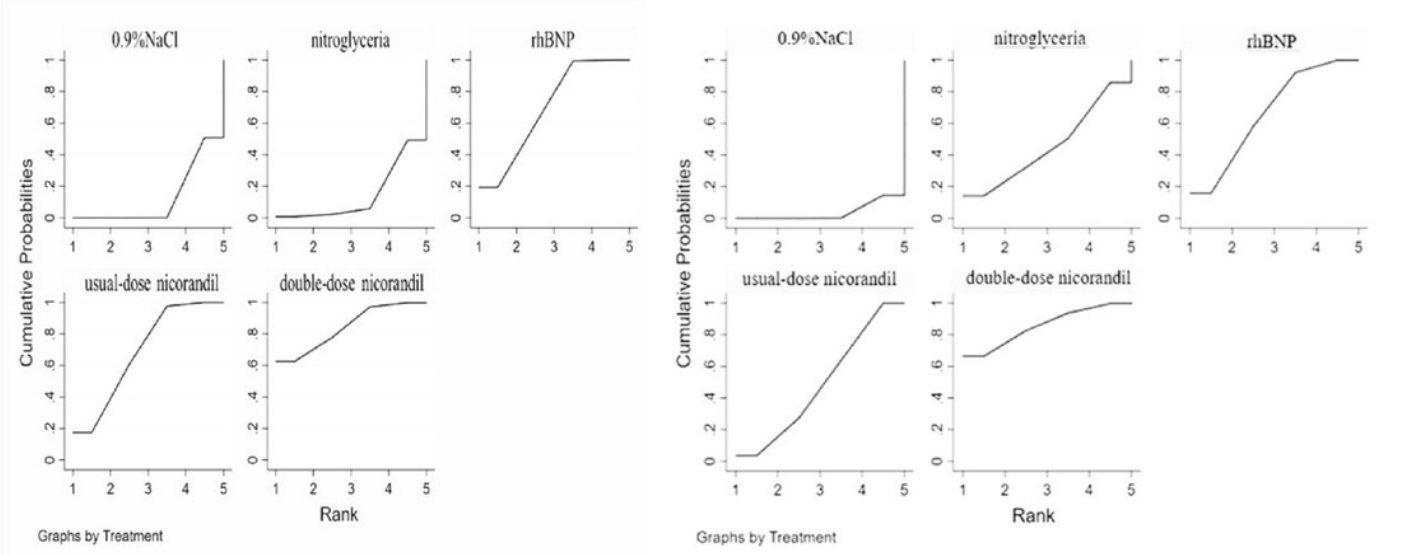

Figure 8

Comparison-adjusted funnel plots for the efficacy of the included agents. A=intravenous saline alone; B=nitroglycerin; C=rhBNP; D=usual-dose nicorandil; E=double-dose nicorandil

Comparison-adjusted funnel plots for the efficacy of the included agents. A=intravenous saline alone; B=nitroglycerin; C=rhBNP; D=usual-dose nicorandil; E=double-dose nicorandil

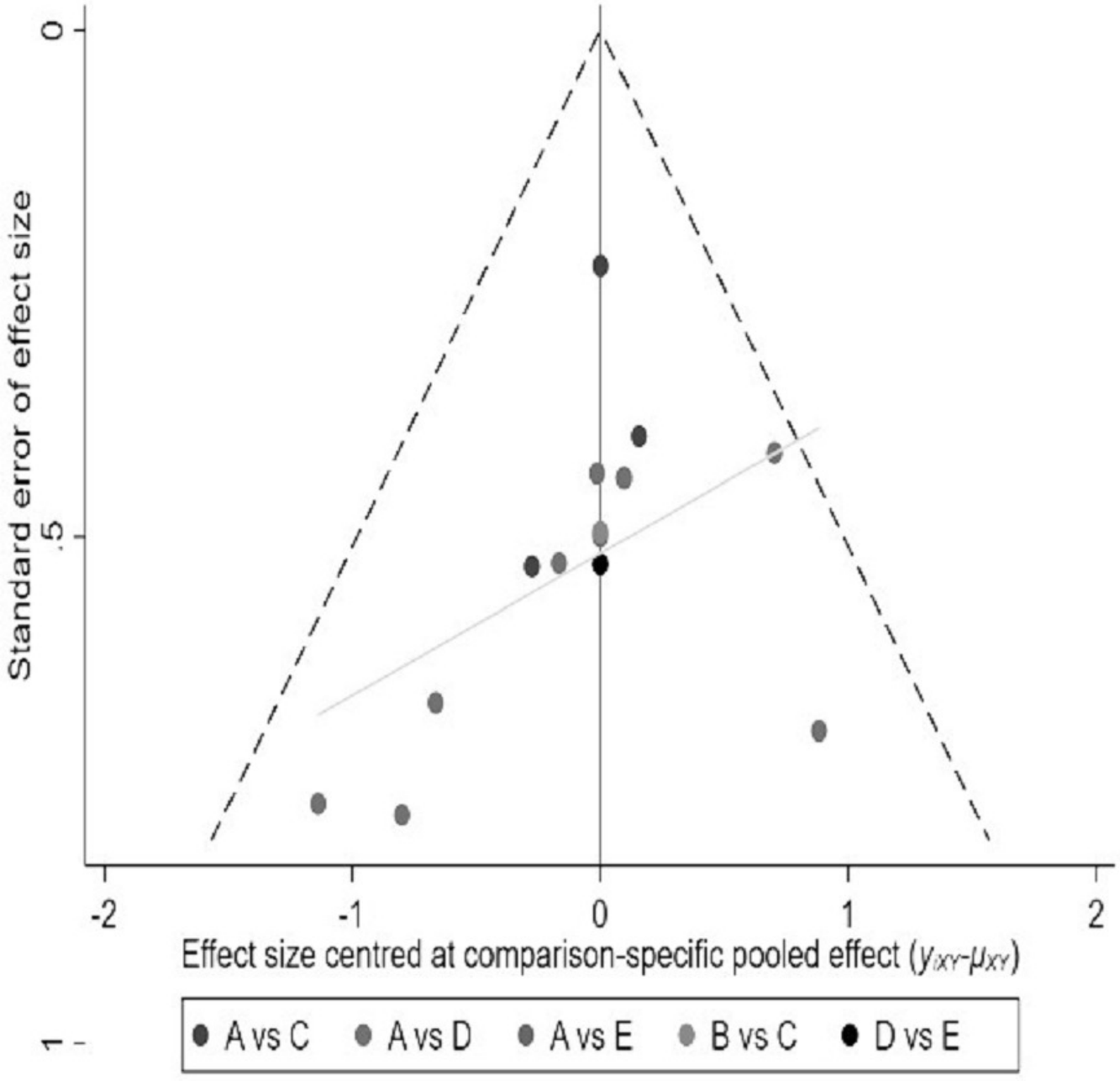
Standard error of effect size
0
.5
1
-2
-1
0
1
2
Effect size centred at comparison-specific pooled effect (y_{ixy}-μ_{xy})
A vs C
A vs D
A vs E
B vs C
D vs E

Table 1(on next page)

Characteristics of include studies

Characteristics of include studies

1 Table1: Characteristics of include studies

Author /year	*Size*	*Follow-up*	*Age*	*Study type*	*Interventions (no.)*	*Comparisons*	*Outcomes*	*Measures*	*Risk of bias*
Liu/2014	1000	7days	67y	RCT	0.9%NaCl(1mL/kg/h)(n=500) rhBNP(0.005ug/kg/min)(n=500)	rhBNP vs 0.9%NaCl	BUN, Scr, eGFR, CIN occurrence	odds ratio Mean±SD	
Liu/2015	209	1 month	69y	RCT	0.9%NaCl(1mL/kg/h)(n=103) rhBNP(0.005ug/kg/min)(n=106)	rhBNP vs 0.9%NaCl	Scr, eGFR, CIN occurrence	odds ratio Mean±SD	
Sun/2015	126	72h	60y	RCT	0.9%NaCl(1mL/kg/h)(n=63) rhBNP(1.5ug/kg)(n=63)	rhBNP vs 0.9%NaCl	Scr, CCl, CIN occurrence	odds ratio Mean±SD	
Xing/2015	116	72h	64y	RCT	nitroglycerin(20ug/min)(n=59) rhBNP(1.5ug/kg)(n=57)	rhBNP vs nitroglycerin	Scr, eGFR, Cys-C, CIN occurrence	odds ratio Mean±SD	
Zhang/2010	149	7days	65y	RCT	0.9%NaCl(0.5-1.5mL/kg)(n=75) rhBNP(1.5ug/kg)(n=74)	rhBNP vs 0.9%NaCl	Scr, eGFR, CIN occurrence	odds ratio Mean±SD	
Fan/2016	240	72h	67y	RCT	0.9%NaCl(1mL/kg/h)(n=120) nicorandil(10mg)(n=120)	nicorandil vs 0.9%NaCl	Scr, eGFR, Cys-C, CIN occurrence	odds ratio Mean±SD	
Fan/2019	252	72h	63y	RCT	0.9%NaCl(1mL/kg/h)(n=125) nicorandil(10mg)(n=127)	nicorandil vs 0.9%NaCl	Scr, eGFR, Cys-C, CIN occurrence	odds ratio Mean±SD	
Iranirad/2017	128	72h	61y	RCT	0.9%NaCl(1mL/kg/h)(n=64) nicorandil(10mg)(n=64)	nicorandil vs 0.9%NaCl	Scr, eGFR, CIN occurrence	odds ratio Mean±SD	
Ko/2013 NCT01103336	166	48h	71y	RCT	0.9%NaCl(100mL)(n=85) nicorandil(12mg)(n=81)	nicorandil vs 0.9%NaCl	Scr, eGFR, CIN occurrence	odds ratio Mean±SD	
Nawa/2015 UMIN000008544	213	1 month	70y	RCT	0.9%NaCl(1.1mL/kg/h)(n=107) nicorandil(0.096mg/mL)(n=106)	nicorandil vs 0.9%NaCl	Scr, eGFR, Cys-C, CIN occurrence	odds ratio Mean±SD	
Zeng/2019	330	48h	66y	RCT	0.9%NaCl(1.1mL/kg/h)(n=112) usual-dose nicorandil(15mg)(n=107) double-dose nicorandil(30mg)(n=111)	usual-dose nicorandil vs 0.9%NaCl double-dose nicorandil vs 0.9%NaCl	BUN, Scr, eGFR, Cys-C,CIN occurrence	odds ratio Mean±SD	
Zhang/2019	250	72h	67y	RCT	0.9%NaCl(1.0mL/kg/h)(n=125) nicorandil(10mg)(n=125)	nicorandil vs 0.9%NaCl	BUN, Scr, crCl CIN occurrence	odds ratio Mean±SD	

Zhang/2019	300	72h	67y	RCT	0.9%NaCl(1.0mL/kg/h)(n=150) nicorandil(10mg)(n=150)	nicorandil vs 0.9%NaCl	BUN, Scr, Cys-C CIN occurrence	odds ratio Mean±SD

BUN: Blood urea nitrogen; Scr: Serum creatinine; eGFR: Estimated glomerular filtration rate; CIN: Contrast-induced nephropathy

Table 2(on next page)

Baseline of studies included population

Baseline of studies included population

1 Table2: Baseline of studies included population

Author /year	Liu/2014		Liu/2015		Sun/2015		Xing/2015		Zhang/2010		Zeng/2019		
Characteristic	0.9%NaCl	rhBNP	0.9%NaCl	rhBNP	0.9%NaCl	rhBNP	nitroglycerin	rhBNP	0.9%NaCl	rhBNP	0.9%NaCl	usual-dose nicorandil	double-dos nicorandil
Number	500	500	103	106	63	63	59	57	75	74	112	107	111
Age- years±SD	65±8.7	68±9.2	69.8±6.7	67.6±7.2	60.37±9.26	59.35±9.01	58.64±11.51	58.91±9.81	67.27±7.07	65.39±7.51	66.69±7.33	67.09±6.85	65.37±7.19
Male (%)	337(67.4)	347(69.2)	63(61.2%)	70(66.0%)	39(61.9)	38(60.3)	40(67.80)	41(71.93)	53(67.7)	52(73.4)	67(39.8)	73(68.2)	78(70.2)
Body mass index	25.2±5.2	23.7±4.5	25.4±4.2	24.9±5	24.1±3.4	23.8±3.7	26.78±3.77	27.16±4.42	NA	NA	24.60±3.34	24.85±2.63	24.67±3.10
Diabetes mellitus(n%)	244(48.8)	256(51.2)	71(68.9%)	76(71.7%)	18(28.6)	13(20.6)	15(25.42)	18(31.58)	18(24)	24(32.4)	18(16.1)	21(19.6)	19(17.1)
Hypertension(n%)	276(55.2)	293(58.6)	59(57.3%)	62(58.5%)	41(65.1)	38(60.3)	35(59.32)	31(54.39)	NA	NA	59(52.7)	69(64.5)	42(37.8)
LVEF (%)	51±4.4	53±4.6	58.4±10.5	61.1±8.2	61.51±2.97	61.81±3.12	47.43±7.20	44.95±7.80	39.67±4.76	39.14±3.87	9(8.0)	5(4.7)	13(11.7)
Drugs													
ACEI/ARB (%)	NA	NA	NA	NA	23 (36.5)	23(36.5)	44(74.58%)	39(68.42%)	59(78.7)	61(81.3)	46(41.1)	56(52.3)	56(50.5)
β-block (%)	NA	NA	NA	NA	49(77.8)	44(69.8)	43(72.88%)	48(84.21%)	17(22.7)	21(28.4)	93(83.8)	80(74.8)	81(73.0)
Statin (%)	491(98.2)	480(96)	102(99%)	103(97%)	NA	NA	56(94.92%)	56(98.25%)	NA	NA	NA	NA	NA
Clopidogrel (%)	500(100)	500(100)	NA	NA	NA	NA	48(81.36%)	51(89.47%)	NA	NA	112(100)	107(100)	111(100)
CCB	NA	NA	NA	NA	24(38.1)	16(25.4)	31(52.54%)	23(40.35%)	NA	NA	NA	NA	NA
Aspirin, n (%)	500(100)	500(100)	NA	NA	NA	NA	NA	NA	NA	NA	112(100)	107(100)	111(100)
CAG, n (%)	175(35)	156(32.2)	36(35%)	33(31.1%)	NA	NA	NA	NA	NA	NA	NA	NA	NA
PCI, n (%)	325(65)	344(68.8)	67(65%)	73(68.9%)	NA	NA	NA	NA	NA	NA	NA	NA	NA

2

3

4

5 Table2: Baseline of studies included population

Author/year	Fan/2016		Fan/2019		Iranirad/2017		Ko/2013		Nawa/2015		Zhang/2019		MD, Zhang/2019	
Characteristic	0.9%NaCl	nicorandil	0.9%NaCl	nicorandil	0.9%NaCl	nicorandil	0.9%NaCl	nicorandil	0.9%NaCl	nicorandil	0.9%NaCl	nicorandil	0.9%NaCl	ni
Number	120	120	125	127	64	64	85	81	107	106	125	125	150	1
Age- years±SD	67.37±6.33	66.07±6.37	65.87±17.62	62.25±16.63	57.64±12.42	61.35±11.77	69.1±10.3	70.8±9.6	70.1±8.1	70.4±7.7	67.11±7.19	67.25±6.42	67.0±7.2	6
Male (%)	95(79.17)	88(73.33)	67(53.60)	76(59.84)	40(62.5%)	39(60.9%)	51(67.1)	53(72.6)	74(78.7)	80(81.6)	114(76.0)	118(78.7)	89(71.2)	9
Body mass index	22.28±2.98	22.36±2.19	23.78±5.98	24.35±5.87	27.78±4.8	28.43±5.6	24.8±3.7	24.1±3.2	23.5±2.9	23.4±3.4	25.10±2.02	24.80±2.17	25.1±2.0	2
Diabetes mellitus(n%)	62(51.67)	66(55.00)	75(60)	81(63.78)	26(40.6%)	27(42.2%)	42(55.3)	30(41.1)	NA	NA	NA	NA	29(23.2)	2
Hypertension(n%)	74(61.67)	69(57.50)	62(49.6)	68(53.54)	41(64.1%)	35(54.7%)	61(80.3)	57(78.1)	NA	NA	71(47.3)	69(46.0)	NA	N
LVEF (%)	51.15±6.36	50.36±5.29	53.58±12.77	51.39±10.35	49.14±5.8	48.87±6.8	NA	NA	NA	NA	60.10±6.88	60.11±7.77	NA	N
Drugs														
ACEI/ARB (%)	47(39.17)	56(46.67)	44(35.20)	46(36.22)	NA	NA	43(56.6)	47(64.4)	10(10.6)	4(4.1)	132(88.0)	134(89.3)	111(88.8)	1
β-block (%)	94(78.33)	101(84.17)	53(42.40)	61(48.03)	NA	NA	35(46.1)	42(57.5)	23(23.4)	35(35.7)	118(78.7)	116(77.3)	111(88.8)	1
Statin (%)	112(93.33)	110(91.67)	83(66.40)	89(70.08)	NA	NA	43(56.6)	37(50.7)	NA	NA	139(92.7)	136(90.7)	NA	N
Clopidogrel (%)	NA	NA	79(63.20)	83(65.35)	NA	NA	NA	NA	NA	NA	150(100)	150(100)	NA	N
CCB	34(28.33)	28(23.33)	56(44.80)	50(39.37)	NA	NA	36(47.4)	34(46.6)	NA	NA	NA	NA	21(16.8)	1
Aspirin, n (%)	NA	NA	101(80.80)	108(85.04)	NA	NA	NA	NA	NA	NA	150(100)	150(100)	NA	N
CAG, n (%)	75(62.50)	68(56.67)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	N
PCI, n (%)	27(22.50)	31(25.83)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	N

Table 3(on next page)

Ranking the CIN incidence of all included agents

Ranking the CIN incidence of all included agents

Table3 Ranking the CIN incidence of all included agents

Treat	SUCRA	PrBest	MeanRank
0.9%NaCl	12.8	0.0	4.5
nitroglyceria	14.5	0.8	4.4
rhBNP	69.5	19.3	2.2
usual-dose nicorandil	68.9	17.4	2.2
double-dose nicorandil	84.3	62.5	1.6

Table 4(on next page)

Ranking the Scr reducing levels of all included agents

Ranking the Scr reducing levels of all included agents

Table4 Ranking the Scr reducing levels of all included agents

Treat	SUCRA	PrBest	MeanRank
0.9%NaCl	3.7	0.0	4.9
nitroglyceria	45.7	14.2	3.2
rhBNP	66.5	15.9	2.3
usual-dose nicorandil	48.6	3.6	3.1
double-dose nicorandil	85.6	66.4	1.6

Table 5(on next page)

inconsistency assessment of all comparisons

inconsistency assessment of all comparisons

1

2 Table5 inconsistency assessment of all comparisons

Side	Direct		Indirect		Difference		P
	Coef	Std	Coef	Std	Coef	Std	
0.9%NaCl	-1.044	0.188	-0.688	612.098	-0.355	612.098	1.000
rhBNP							
0.9%NaCl	-1.031	0.499	-2.722	0.916	1.691	0.939	0.072
double-dose nicorandil							
nitroglyceria	-1.062	0.495	-1.887	1707.83	0.826	1707.83	1.000
rhBNP							
usual-dose nicorandil	-0.657	0.527	1.034	0.869	-1.691	0.939	0.072
double-dose nicorandil							

3